The Brain in pain: The neurophysiology of chronic pain in CFS/ME

Report to Action for M.E. Research Panel

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Activities/Deliverables	Numbers achieved / Activities achieved	RAG Rating[1]	Comments /Next steps/ Actions required
CFS patients recruited	15 of 15		Completed
Sensory tests (CFS patients)	19 of 15		This figure includes 3 patients that were not centrally sensitised and so could not be included in the scanning part of the project
MRI scans (CFS patients)	47 of 45 (3 scans each)		This includes two unusable scans of a patient that had to be excluded. Not included are scans cancelled at short notice that were still charged by the imaging centre.
Control recruited	19 of 15		This included 4 controls who were unable to complete all 3 scans, for various reasons (we over-recruited to compensate for this). Not included are scans cancelled at short notice that were still charged by the imaging centre.
Sensory tests (controls)	19 of 15		This includes one control who failed to attend for scanning appointments and was excluded from further involvement.
MRI scans (controls)	51 of 45 (3 scans each)		This includes the 4 controls that were unable to complete the protocol.

	Difficulties/issues that will affect/have affected target delivery		Some difficulties/issues that may affect meeting target		All on target/no issues or difficulties/target met on time

Project 1

Table 1: The detection of central sensitisation in CFS and fibromyalgia.

Table 1: participant characteristics for project 1	Healthy controls	Chronic Fatigue Syndrome	Fibromyalgia
Total participants	19	19	18
Median age (range)	34.0 (23-55)	37.0 (19-62)	49.0 (23-64)
Mean age (standard deviation)	35.2 (9.1)	38.4 (11.4)	43.1 (12.1)
M:F (%age male)	6:13 (32%)	7:12 (37%)	4:14 (22%)
CS:non-CS	0:19	16:3	17:1
%age with CS	0	84	94

CS: centrally sensitised; non-CS: non-centrally sensitised; The determination of central sensitisation required positive results on tests of both temporal summation and diffuse noxious inhibitory controls (DNIC) or conditioned pain modulation (CPM). No participant showed CS on one test but not another.

Pain phenotypes were determined in all participants by a standardised battery of quantitative sensory tests (QST). These tests are able to detect central sensitisation, a hypersensitivity of the central nervous system proposed to underlie the pathophysiology of both chronic fatigue syndrome (CFS) and fibromyalgia (Bourke, Langford et al. 2015). The QST focussed on measures of diffuse noxious inhibitory controls or conditioned pain modulation (Table 2) and temporal summation (Table 3). Prior studies in CFS and fibromyalgia have typically relied upon either DNIC or temporal summation to demonstrate central sensitisation (Bourke, Langford et al. 2015). This is the first ever study to use both tests on the same subjects, and both had to be positive in order to confirm central sensitisation. In actual fact, all participants who showed CS on one test also showed the same on the other test. This provides an immediate test of validity of these findings.

Central sensitisation was present in the majority of both case groups and this finding was statistically significant (Table 2). A similar proportion of the fibromyalgia group (94%) demonstrated central sensitisation compared with the CFS group (84%), with no significant difference in the comparison between the case groups (Table 2).

Table 2: Diffuse noxious inhibitory controls (DNCIC)/Conditioned pain modulation (CPM)	Healthy controls (19) v Chronic fatigue syndrome (18)	Healthy Controls (19) v Fibromyalgia (19)	Chronic fatigue syndrome (18) v Fibromyalgia (19)
Mann Whitney-U	$p<0.001$*	$p<0.001$*	$p = 0.27$
Unpaired t-test	$p<0.001$*	$p<0.001$**	$p = 0.43$

* *Results reach significance at $p<0.05$ Statistical tests show results of comparisons or differences in raw data across each test for each group, rather than proportions.*

Table 3: Temporal summation	Healthy controls (19) v Chronic fatigue syndrome (18)	Healthy controls (19) v Fibromyalgia (19)	Chronic fatigue syndrome (19) v Fibromyalgia (18)
Mann Whitney – U	p<0.001*	p<0.001*	p = 0.30
Unpaired t-test	p<0.001*	p<0.001*	p = 0.54

* *Results reach significance at p<0.05 Statistical tests show results of comparisons or differences in raw data across each test for each group, rather than proportions.*

Although central sensitisation has been proposed as being central to these disorders (Phillips and Clauw 2011, Bourke, Langford et al. 2015), there has been very little work done in this area to confirm this. Groups that have reported on QST studies in these disorders have either relied upon pain thresholds or temporal summation alone to define central sensitisation (Phillips and Clauw 2011, Bourke, Langford et al. 2015). However, lower pain thresholds in cases as compared to controls is not synonymous with central sensitisation and the presence of temporal summation is not the same as the presence of a centrally sensitised state (Woolf 1996). The further strength of this study is that we took particular care to exclude patients with comorbid psychiatric disorders, and also excluded patients who were taking medications that might have confounded these findings. These precautions provide further confidence that central sensitisation is specific to these disorders, and not the result of confounding factors.

This is the first study, to the authors' knowledge, that has provided clear and validated evidence of the presence of central sensitisation in both CFS and fibromyalgia. It is also the first study to compare fibromyalgia and chronic fatigue syndrome in this regard. When these findings are considered in the light of the existing literature, we would suggest that central sensitisation is present and detectable in the large majority of sufferers of both these disorders (Bourke, Langford et al. 2015).

The clinical relevance of central sensitisation in CFS and fibromyalgia is twofold – firstly in that QST are essentially bedside tests and can be performed in the clinic; the second is that it may have potential as a therapeutic drug target, defining a physiological abnormality that may be moderated by pharmacological correction. This is something that our group have started to investigate in fibromyalgia (Wodehouse, Casey et al. 2015). Although its origins are in pain medicine, central sensitisation may also be able to explain symptoms other than pain, including the cluster of symptoms arising in CFS and fibromyalgia (Bourke, Langford et al. 2015). As such, any medication that is able to adequately reverse central sensitisation may be capable of treating chronic pain in CFS and fibromyalgia but also other symptoms such as fatigue and post-exertional malaise.

Project 2: The neurophysiology of chronic pain in CFS and fibromyalgia

Table 4: participant characteristics for project 2	Healthy controls	Chronic fatigue syndrome	Fibromyalgia
Total participants	18	15	15
Median age (range)	33.5 (23-55)	36.0 (23-64)	43 (22-62)
Mean age (standard deviation)	34.1 (+/-9.0)	41.5 (+/-12.8)	39.6 (+/-11.6)
M:F (%age male)	5:13 (28%)	4:11 (27%)	4:11 (27%)

Our aim was to investigate the mu-opioid and D2-dopamine neurotransmitter systems for dysregulation in response to pain in the two case groups.

We achieved this using a pharmaco-fMRI repeated measures design, with the delivery of an acute, moderately painful (supra-pain threshold) stimulus during the course of an MRI scan, interspersed with painful (at pain threshold) and non- painful (sub-pain threshold) stimuli. This was repeated in three sequential fMRI scans each combined with one of placebo, naltrexone and amisulpride.

We found no significant difference between cases and controls or between case groups, when comparing responses to pain in placebo, naltrexone, and amilsupride scans. Our findings in the interim analysis conducted at an earlier point in the study that suggested a significant difference between cases and controls likely reflected a type 1 statistical error. Owing to the complexity of the analysis of the imaging study, we are unable to report beyond these results at present.

On-going analyses

Our secondary analysis is underway and we are currently approximately 30% through the analyses. This includes the analysis of genetic and questionnaire data, and examining QST data (central sensitisation) in association with the imaging data.

Clinical implications of the analysis so far

This is the first ever case control study to show that the large majority of patients with CFS show central sensitisation, using not one but two tests of CS, and that this finding is unlikely to be confounded by comorbid conditions or taking medication. Using other funding, we have also been able to show that this is equally the case in patients with fibromyalgia. This might help to explain the well-established overlap between these two chronic pain conditions. These findings need replication with larger samples and by independent scientists, but provide patients and clinicians an explanation of symptoms that can make some sense of these otherwise unexplained common illnesses.

The lack of significant differences between cases and controls on fMRI findings may reflect a type 2 error, but also suggests that mechanisms to explain central sensitisation in CFS and FM do not involve mu-opioid or dopaminergic systems.

Expenditure	**37,093.5**
salary (Imanova RA)	57,356
honorarium	400
QST equipment	3,000
salary (data entry check)	691.61
reimbursement, scans, honorarium	5,619.55
reimbursement, scans, honorarium	12,253.04
stationary, ipad, suppliesm UDS, drugs	977.76
genetic analysis	1,339.7
printing	845
Salary (RA2)	28,514.86

References

Bourke, J. H., R. M. Langford and P. D. White (2015). "The common link between functional somatic syndromes may be central sensitisation." Journal of Psychosomatic Research; http://www.sciencedirect.com/science/article/pii/S0022399915000057.

Phillips, K. and D. J. Clauw (2011). "Central pain mechanisms in chronic pain states--maybe it is all in their head." Best Pract Res Clin Rheumatol **25**(2): 141-154.

Wodehouse, T., L. Casey, K. Poply, V. Anjana-Reddy, J. Bourke, D. Pyne, H. Tahir, K. Ullrich and V.
Mehta (2015). A pilot study investigating whether Quantitative Sensory testing alters after Pregabalin in patients with Fibromyalgia. European Pain Federation (EFIC) Annual Congress. Vienna, Austria.

Woolf, C. J. (1996). "Windup and central sensitization are not equivalent." PAIN **66**(2-3): 105-108.